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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/695,769	10/25/2000	Darwin J Prockop	9598-101U2(99-0356)	4022

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Morgan, Lewis & Bockius, L.L.P  
1701 Market Street  
Philadelphia, PA 19103

EXAMINER

HAMA, JOANNE

ART UNIT PAPER NUMBER

1632

DATE MAILED: 05/18/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

<b>Advisory Action</b> <b>Before the Filing of an Appeal Brief</b>	<b>Application No.</b> 09/695,769	<b>Applicant(s)</b> PROCKOP ET AL.	
	<b>Examiner</b> Joanne Hama, Ph.D.	<b>Art Unit</b> 1632	

**--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --**

THE REPLY FILED 15 December 2005 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:

- a) ☒ The period for reply expires 6 months from the mailing date of the final rejection.
- b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### NOTICE OF APPEAL

2. ☒ The Notice of Appeal was filed on 15 December 2005. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

#### AMENDMENTS

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
- (a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
- (b) ☐ They raise the issue of new matter (see NOTE below);
- (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
- (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

NOTE: \_\_\_\_\_. (See 37 CFR 1.116 and 41.33(a)).

4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☒ Applicant's reply has overcome the following rejection(s): 102.
6. ☐ Newly proposed or amended claim(s) \_\_\_\_\_ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☐ will not be entered, or b) ☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
- The status of the claim(s) is (or will be) as follows:
- Claim(s) allowed: \_\_\_\_\_.
- Claim(s) objected to: \_\_\_\_\_.
- Claim(s) rejected: 1-12,14-29,31-36.
- Claim(s) withdrawn from consideration: \_\_\_\_\_.

#### AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing of good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

#### REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: see attached.
12. ☐ Note the attached Information Disclosure Statement(s). (PTO/SB/08 or PTO-1449) Paper No(s). \_\_\_\_\_
13. ☐ Other: \_\_\_\_\_.

Applicant has filed an After Final response to the Final Action of March 24, 2005 on December 15, 2005. Claims 13, 30, 37-41 are cancelled. Claim 24 is amended.

Claims 1-12, 14-29, 31-36 are under consideration.

### ***Claim Amendment***

It is noted that Applicant has amended claim 24 to fix a typographical error. This amendment has been acknowledged.

### **Withdrawn Rejections**

#### **35 U.S.C. § 102**

Applicant's arguments, see pages 8-10 of Applicant's response, filed December 15, 2005, with respect to the rejection of claims 1-12, 14-29, 31-36 under 35 U.S.C. 102 have been fully considered and are persuasive. It is noted that the reasons for withdrawal of this rejection are discussed below in the maintenance of the 103 rejection, wherein the claims are obvious over Huang et al., 1997, Biotechnology Letters, 18: 89-92. The rejection of claims 1-12, 14-29, 31-36 has been withdrawn.

### **Maintained Rejections**

#### ***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the

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invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1-12, 14-29, 31-36 remain rejected under 35 U.S.C. 103(a) as obvious over Huang et al., 1997, Biotechnology Letters, 18: 89-92, for reasons of record, March 24, 2005 and August 10, 2004.

### ***Response to Arguments***

Applicant's arguments filed December 15, 2005 have been fully considered but they are not persuasive.

Regarding the issue that Huang teaches only one out of three cell lines plated at low densities results in cell growth (Applicant's response, page 9, parag. following citation from MPEP § 2112), it should be pointed out that one out of the three cell lines grew when the cells were plated at 2.8 cells/cm<sup>2</sup> (see also Office Action, August 10, 2004, page 7, 1<sup>st</sup> parag.). Huang indicates that when cells were plated more densely, more colonies grew. Huang teaches that when cells were plated at 50 cells/well (i.e. 28 cells/cm<sup>2</sup>) 4 colonies grew; when cells were plated at 500 cells/well (i.e. 280 cells/cm<sup>2</sup>), 28 colonies grew. Huang indicates that there is cell density-dependent proliferation of these stromal cells. Huang's teachings indicate that should an artisan have plated cells at 50 cells/cm<sup>2</sup>, (i.e., 88.5 cells/well) that the cells would have grown. Regarding the issue of replating the cells (Applicant's response, page 9, 3<sup>rd</sup> parag.), as Huang does not outright teach replating cells, the rejection is no longer a 102 rejection. It does, however, remain a 103 rejection because it is well known in the art that when cells are

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confluent, that unless cells are split and replated, they will die. That said, regarding the issue that Huang teaches that only five LC3 or 50 LC3 cells plated on a 1.77 cm<sup>2</sup> culture dish results in the formation of one colony or four colonies and that it is unclear how many cells are in a colony (Applicant's response, page 10, 2<sup>nd</sup> and 3<sup>rd</sup> parag.) and it would be impossible to determine if each and every element of the claims recited in Huang is anticipated, an artisan would have replated the cells taught by Huang when the cells reached confluence.

Regarding the issue that Huang only teaches one example of cells that grew at a density of 2.8 cells/cm<sup>2</sup> (LC3) (Applicant's response, page 11, 3<sup>rd</sup> parag. under "Rejection of claims 1-2, 14-29, and 31-36..."), it should be pointed out that a second line, LC2, was able to grown in conditioned media (Huang, page 91, 1<sup>st</sup> col., 2<sup>nd</sup> parag.). While Applicant points out that certain cell lines do not grow when plated, it should be pointed out that of the ones that did grow are the examples that being applied to demonstrate that the claims are obvious. Applicant indicates that Huang does not teach how many cells are in a colony and that Huang provides no teaching or suggestion that replating the cells would result in a 10-fold expansion of those cells (Applicant's response, page 12, 1<sup>st</sup> parag.). In response, as indicated above, be that it may that it is unknown how many cells are in a colony, an artisan would have replated cells when the culture was confluent and replated cells would be a way of expanding the cells of interest.

As such, the claims remain rejected.

Claims 1, 22-29, 31-36 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Huang in view of Kuznetsov et al., 1997, J. Bone and Mineral Res., 12: 1335-1347, Azizi et al., 1998, PNAS, USA., 95: 3908-3913, Greenberger (U.S. Patent 5,766,950), and Prockop, 1997, Science, 276: 71-74, for reasons of record, March 24, 2005 and August 10, 2004.

### ***Response to Arguments***

Applicant's arguments filed December 15, 2005 have been fully considered but they are not persuasive.

Applicant indicates that Huang discloses an initial plating density within the scope of the present claims, but does not teach nor suggest replating the cells or replating the cells such that the cells are expanded by a factor of 10-fold. In response, as described above, it would have been obvious to an artisan to split and replate cells once they have been confluent. Further, splitting and replating cells is a common way of expanding a cell line in culture. Regarding the teachings of Kuznetsov, the point of the citation was to indicate that human marrow stromal fibroblast (HMSF) cells could be plated at low densities (as low as 7 cells/cm<sup>2</sup>) and that the cells can be passaged. Regarding Azizi, Greenberger, and Prockop, these citations were to indicate that there are a variety of cytokines and growth factors that can be used to grow and expand marrow stromal cells such that an artisan could obtain cells plated at a low density and be expanded to large numbers. Thus, in view of these teachings, an artisan would have arrived at the claimed invention.

As such, the rejection to these claims remain.

No claims allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joanne Hama, Ph.D. whose telephone number is 571-272-2911. The examiner can normally be reached Monday through Thursday and alternate Fridays from 9:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, Ph.D. can be reached on 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

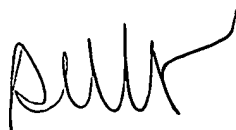
Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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JH

A handwritten signature in black ink, appearing to be 'P. H. K.' or similar, with a stylized, cursive script.